Original Article

# Some Prediction Models in the Study of Diabetic Retinopathy among known Type II Diabetes Mellitus Patients in a Southern Part of India: Various Statistical Models Approach

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## Abstract

**Background:** Diabetic Mellitus is a chronic disease and metabolic disorder. DM affects about 180 million people in the presently and it is a public health problem in worldwide. To find out the risk factors and how much its influence, to identify the risk factors that influencing, to identify the presence of DR and its progression by forming mathematical equations using which was found possible with some variables and to find several stages of DR and its progression.

**Materials and Methods:** In this study, adult population (age ≥ 18) only was taken into account for data analysis. Some structured questionnaires were used for data collection. We have done some hospital based retrospective studies among known T2DM patients. The continuous variables were expressed as mean and standard deviation and categorial variables as frequency and proportions. We have used, various prediction statistical models.

**Results:** By multiple regression analysis, found the influencing factors in the progression of DR, predicted the probability of a T2DM patient to develop DR and found the probability of DR among diabetes up to a given period of time and using by Markov Chain Analysis found the TPM and the absorbing state in a T2DM patient and to identify as having complete vision loss.

**Conclusions:** Statistical models were revealed that found the influenced factors and risk ratio has been computed, Number of years of DM, and progression and transition of DR which predict the chance to develop DR in a known T2DM patient.

**Key Words:** diabetic retinopathy, duration of diabetes, hypertension, family history, various multiple logistic regression models,

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## Introduction

Diabetes mellitus (DM) is known as diabetes. DM is a chronic disease metabolic disorder [1] DM caused by deficiency in the production of insulin by pancreas in the human body. DM is a metabolic disorder due to high blood sugar levels over a long period in human blood. DM also caused 1.6 million deaths in 2016. As per WHO report, DM was the 7$^{th}$ cause of mortality in 2016. [2] In some studies, blindness from DM is almost entirely preventable by early diagnosis, controlling risk factors and timely treatments with ophthalmologist. [3, 4] The disease is classified into two according to the distinct groups of patients. [5] Two types of DM are, Type1DM and Type2DM. Diabetic Retinopathy [6] (DR) is a microvascular complication of DM Cheung et al. [7] DR is also called "eye threatening disease". As per WHO, five percentage of world population nearly five million people were blinded due to DR in 2002. [2] One third of times more chance of getting blindness in diabetics than non-diabetics. DR is causing vision loss in worldwide and nearly three fourth of population were affected those who were living in under developing income countries [8] and Tapp et. al. [9] DR is a very worst difficulty, and all parts of diabetic eye will be affected as shown in [**Figure-1**]. Main factors for development of DR are duration of DM, glycemic control, age, sex, high blood pressure, kidney diseases, heredity, lipids profiles, malnutrition, puberty, poverty, pregnancy [4] in a study by Chakrabarti et al. [10] Duration of DM and glycemic control had direct and indirect correlation with DR. Hypertension is also an increasing risk of DR in T2DM patients. The main objectives were to find out the risk factors and how much its influence in the development of DR, to identify the risk factors that influencing in the progression of DR, to identify the presence of DR and its progression by forming mathematical equations using which was found

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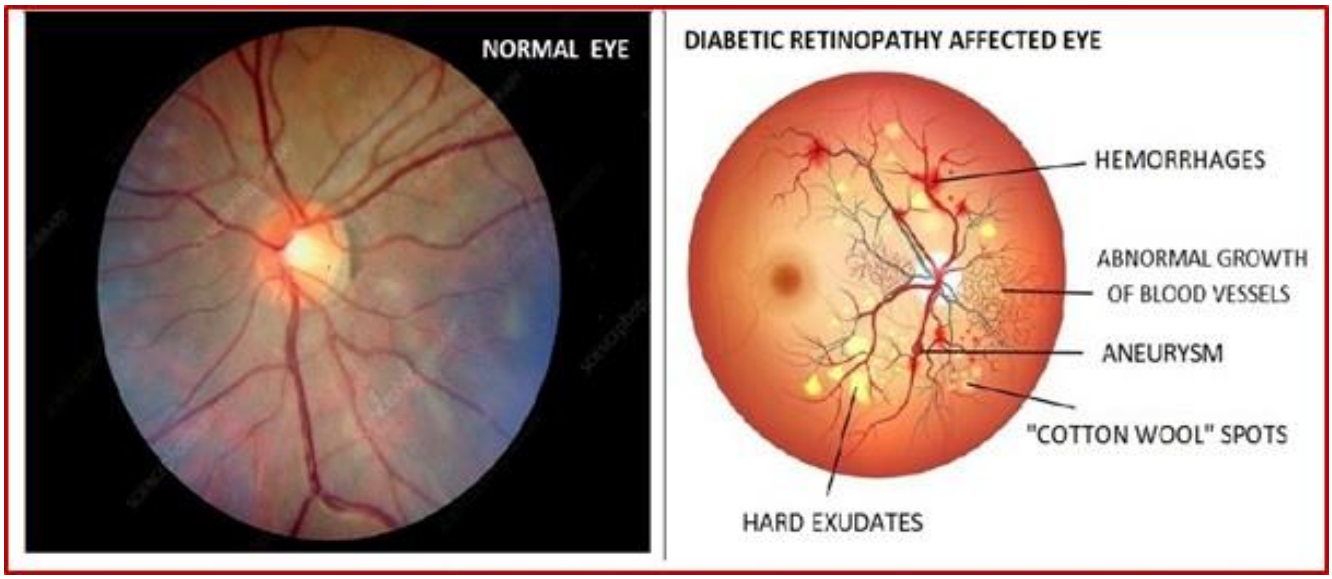
**Figure – 1 View of Normal Eye and Diabetic Retinopathy Eye**




possible to the development of DR with some variables and to find the several stages of DR and its progression.

## Study design, population, sample size and study variables:

We have done some hospital-based retrospective studies in Amrita Institute of Medical Sciences, Kochi, and Aravind Eye Hospital, Thavalakuppam, Puducherry from January – April, 2017, July – September 2017 and in January – April 2018. In these studies, we used four different statistical models: Model-1: Multiple Linear Regression analysis (MLR), [12] Model-2: Binary Logistic Regression analysis (BLR), [14] Model-3: Cox's Regression analysis [15] and Model-4: Markov Chain (MC) analysis. [16]

## Data collection:

Data were collected from patients' medical records with an inclusion patient with ≥18 years. In these studies, we considered factors like age, sex, duration of diabetics, level of Hemoglobin $A_1C$ ($HbA_1C$), high-density lipoprotein (HDL), triglycerides, family history of DR, hypertension (high blood pressure), [8] and low-density lipoprotein (LDL), Optical Coherence Tomography (OCT) value, [13] stages of DR and other problems like high blood pressure, family history of DR and neurological problems. [11]

## Models used:

In model-1 [12] 250 known T2DM patients' details were collected in the period of January to April, 2017 with aged ≥18 years with an inclusion criterion of those who were permanent residence of Kerala area, an exclusion criterion of those who were had severe chronic and communicable, other non-communicable diseases. Samples were collected by using simple random sampling method from the patients' data base. In that, 125 patients were with DR and 125 without DR. Y = OCT value (in µm) is to be taken as dependent variable.

The independent variables are Age taken as $X_1$ (in years), Gender($X_2$): Male = 1, Female = 0, $HbA_1C$ as $X_3$ (%), Duration of DM as $X_4$ (in years), Triglyceride as $X_5$ (mg/dl), HDL as $X_6$ (mg/dl), Family History ($X_7$) retinopathy in their family = 1, otherwise = 0, Hypertension as $X_8$, if patient had high blood pressure = 1, otherwise 0, LDL as $X_9$ (in mg/dl). OCT is an imaging technology which can uses low coherence light to cover micrometer resolution and imaging in biologic tissues. [13] By this model, significant variables, ANOVA test for goodness of fit and R-Square value were found. F-value not significant, then the model was good fit for prediction in the development of DR. It measures macular edema thickness (MET). [6] We could write multiple variable equation as, $Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots \ldots \ldots + \beta_{11} X_{11} \ldots\ldots\ldots\ldots$ (1). Fix all values of β multiplier and to find out MET.

In model-2, [14] 250 T2DM patients' data from medical records in the period of July to September 2017 with inclusion criteria of aged ≥18 years and those who were residing minimum one year in Kochi area, those who were had severe chronic and other communicable diseases. Samples were collected consecutively by using simple random sampling method from the patients' data base. In this approach Y as dependent variable. If an individual having DR then, Y = 1, otherwise = 0 (without DR). Independent variables were, Age ($X_1$) taken as in years; Sex ($X_2$) = 1 (male), Female = 0; $HbA_1C$ ($X_3$); Pre-Prandial sugar level ($X_4$); Post-Prandial sugar level ($X_5$); Systolic Blood pressure, ($X_6$); Diastolic Blood

pressure ($X_7$); Duration of diabetes ($X_8$); Serum triglycerides ($X_9$); Serum HDL-cholesterol ($X_{10}$); Family History of DR ($x_{11}$) = 1, otherwise = 0. Significant variables were found by bivariate Chi-Square test and the other variables with $p<0.20$ were included in the final BLR analysis with step-wise elimination method. By BLR model, we have identified the influencing factors of DR. For goodness of fit, Hosmer-Lemeshow (H-L) test was used. In H-L test, $X^2$-test wasn't significant meant the selected variables were good fitted to BLR equation.

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \dots\dots\dots + \beta_{11} X_{11}\ ^{[14]} \text{ ---------- (1)}$$

Substitute, $x_1, x_2, \dots\dots\dots, x_{11}$ in the equation and to find 'Y' value and $e^Y$. Then, the odds ratio by using,

$$\frac{P}{1-P} = e^Y \text{ ---------- (2)}$$

and p–value is to be found. Hence, one could get the chance for development of DR in a DM patient.

In model-3, [15] I have included thirty DR patients' data in the period of July to August 2018 from AIMS, Kochi. Recorded their difficulties like high blood pressure ($X_1$), family history of DR ($X_2$) and neurological disorder ($X_3$) were taken as binary values as $X_1$, $X_2$ and $X_3$. Sample were collected by simple random sampling with inclusion criteria those who were had the above mentioned 3 problems with aged ≥ 30 years and those who were living one year and above in Kochi. Exclusion criteria of those weren't have the above-mentioned problems and any other heart problems/complications. If a patient had no problem, then covariate taken (0, 0, 0) and hand all (1, 1, 1). Totally there were eight covariate combinations (1,1,1), (1,0,1), (0,1,0), (0,0,1), (0,1,1), (1,0,0), (1,1,0), and (0,0,0). To find $\beta_1$, $\beta_2$, and $\beta_3$ by solving Cox's partial likelihood [15] is as follows,

$$P_L^{[15]} = \prod_{i=1}^{k} \frac{e^{\beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3}}{\sum_{k} e^{\beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3}}$$

From the above likelihood function, equations (1), (2), and (3) has been formulated and simplify, then would get the values of

$\hat{\beta}_1, \hat{\beta}_2, \hat{\beta}_3$ other possible covariate combinations have formed. We have to form over all probability to develop DR as:

$$h(t) = h_0(t)\, e^{x1\beta1+x2\beta2+x3\beta3+\dots\dots + xk\beta k}$$

In this, h(t) denotes the overall probability of developing DR; $h_0(t)$ denotes the hazard rate due to past duration of diabetes and $e^{x1\beta1+x2\beta2+x3\beta3+\dots\dots+xk\beta k}$ is the overall hazard rate based on respective DR patient's Covariate combinations. By solving the above equation, then we would get the probability of developing DR up to over a period of time of a T2DM patient.

In model-4 [16] conducted a hospital-based cross-sectional-study with 250 DR patients were collected from Aravind Eye Hospital from January 2017 and January 2018 from patient's records by simple random sampling method with an inclusion of patients ≥18 years and those who were residing ≥1 year in Pondicherry, an exclusion of those who were had other severe diseases and not willing to participate in our study. At every visit, a retinal specialist graded retinal findings using a modification of the Airlie House Classification of Diabetic Retinopathy (AHCDR). [17] AHCDR is the gold standard method on grading of stereo photographs of 7 fields and classifies DR into 13 complex levels ranging from level 10 (no DR) to 85 (severe vitreous hemorrhage). Patients were screened first time in January 2017, and the second screen was done after one year in January 2018 to the same patients and found their DR stages. The four-stages of Markov Chain model for the natural course of DR were taken as shown in **[Figure – 2]**. Markov model is a time-homogeneous distribution by using this estimating transition probabilities by Kalbfleisch and Lawless, [18] and the mathematical symbols for transition probabilities was generated by Chen et al. [19] I have classified NPDR into further classifications and formed six-stages of MC model for the natural progress of DR as shown in **[Figure – 3]**. I have taken, stage-1 indicates no retinopathy; stage-2 as micro aneurysms, stage-3 and 4 indicate intermediate stages of background DR, stage-5 as pre-proliferative and stage-6 proliferative retinopathy. Like this, we could formulate the transition rate matrix and its probability matrix for six-stages of DR. From this, we have classified the transition of DR as shown in **[Figure – 4]** and have got the probability of developing DR in a person for 1 and 5 years by forming both transition matrix and TPM.

**Figure – 2 Distribution of four-stages of Markov Chain model for the natural course of DR**

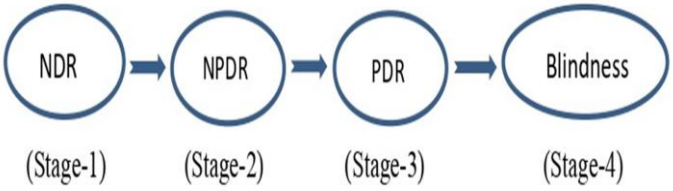
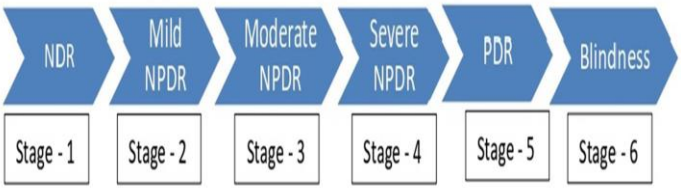



**Figure – 3 Classifications and formed six-stages of MC model for the natural progress of Diabetic Retinopathy**




## Statistical Analysis used:

The quantitative variables were presented as mean, standard deviation, categorical variables as frequency and percentages. In model-1, multiple regression analysis approach was used to find risk factors of DR in a DM patient, how much influence in development of DR have been computed and ANOVA test was used to find goodness of fit. In model-2, binary logistic regression analysis was used to find the risk factors, and a Hosmer-Lemeshow test [20] was used for goodness of fit of this model. In model-3, Cox's regression model [15] was used to evaluate the combined influence of the past duration of presence of DM with other covariate combinations. By this, the probability of developing DR up to a given period of time was calculated. In model-4, we have used Markov chains approach [21, 22] and Markov process [19] was used to estimate the

Transition Probability Matrix (TPM) and the progression of DR. The grading of retinal findings was detected by a trained retinal specialist in retina center on each visit without the knowledge of previous retinal classifications. [23] Data were managed and complied by Microsoft Excel 2010 **[Microsoft Ltd., USA]** and analyzed by SPSS 20.0 version **[IBM SPSS, USA]** and the level of significant was fixed as p–value less than 0.05.

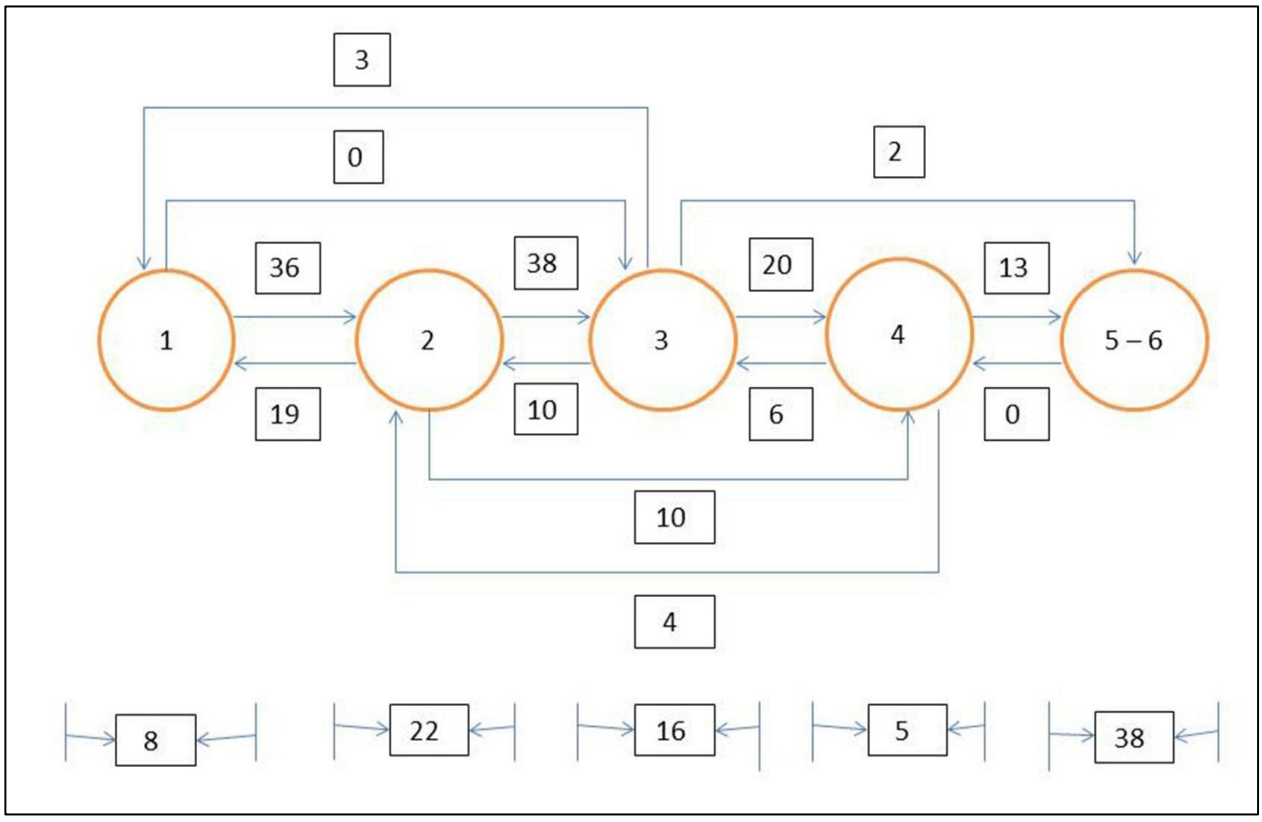
## Ethical Consideration

The studies were done with prior permissions were obtained from both the institutions before conducting these studies. Patients' data were obtained from the medical records and some information from the patients directly. Patients' data were confidential and preserved by both the institutions. Ethical approval from the Institutional Review Board/Ethics Committee of both centers has been obtained and informed all the details about the studies and had got the oral consent was taken from all participants at the time of study period.

## Results

According to model-1, two hundred and fifty T2DM patients with DR patients were included and 133 (53.2%) were male. The average age of T2DM patients was 49.4 ± 11.3 years. The average duration of DM of T2DM patient was 15.3 ± 6.7 years. Mean thickness of the macula was 472.3 ± 128.6 µm. From this model, ANOVA test F-value was 54.724 with $p<0.001$ was statistically very highly significant. So, the model was good fit for prediction in the development of DR and R–square value was 0.79. From this, predict the selected variables for multiple linear regression model would find the influencing factors in the development of DR. Variables, β co-efficients, odds ratios and their significance were listed **[Table-1]**. In multiple linear regression analysis, the variables age, $HbA_1C$, duration of diabetics, triglycerides, family history of DR, hypertension and LDL were significant, gender and HDL were not showed any significant with the development of DR. Based on β co-efficient values, we have

**Figure – 4 Distribution and Classifications of Transition and Stages of Diabetic Retinopathy**




The numbers in the circles indicate the grade of Diabetic Retinopathy; solid bars with arrows to the right, progression; and solid bars with arrows to the left, regression. Bottom, Number of subject observations per year with no change in grade.

**Table: 1 List of influencing variables, their regression co-efficient (β), their level of significance and 95% Confidence Intervals**

| Predictor Variables in the Model | β | Standard Error | Sig. | 95% C.I for β | |
|---|---|---|---|---|---|
| | | | | Lower Bound | Upper Bound |
| Age ($X_1$) | 1.035 | 0.524 | 0.046 | 0.021 | 2.049 |
| Gender ($X_2$) | -6.651 | 11.454 | 0.563 | -29.284 | 15.981 |
| $HbA_1C$ ($X_3$) | 1.387 | 2.468 | 0.036 | -3.503 | 6.277 |
| Duration of diabetics ($X_4$) | 13.631 | 0.746 | 0.0001 | 12.080 | 15.181 |
| Triglycerides ($X_5$) | 0.787 | 0.422 | 0.047 | -0.025 | 1.599 |
| High Density Lipoprotein (HDL) ($X_6$) | 0.139 | 0.443 | 0.765 | -0.776 | 1.053 |
| Family history of DR ($X_7$) | 1.750 | 10.864 | 0.031 | -19.727 | 23.226 |
| Hypertension ($X_8$) | 33.831 | 13.272 | 0.012 | 7.612 | 60.051 |
| Low Density Lipoprotein (LDL) ($X_9$) | 1.027 | 0.514 | 0.043 | 0.033 | 2.022 |
| Constant ($\beta_0$) | 148.840 | 57.636 | 0.013 | | |

**Sig. – Significant ($p<0.05$); N. Sig. – Not Significant ($p>0.05$)**

**H. Sig. – Highly Significant ($p<0.001$); C.I – Confidence Interval**

formed the multiple linear regression equation as follows, $Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots\ldots\ldots + \beta_{11} X_{11}$ ……. (1) Using this equation, to predict the expected value for a DR patient, eighteen years respectively in a DR patient up to given period of time. The high probability of getting DR with all complications was found as 0.862 in the 3rd year and those who had no complications then the probability 0.646 of developing DR was low.

According to model-4, totally two hundred and fifty DR patients were included in this study from Aravind Eye Hospital, Puducherry. Among these DR patients, 176 (70.4%) were male and 74 (29.6%) females. The average age who had diabetes with five and above was 57.4 ± 8.5 years. The numbers of patients of the stages of DR were indicated in circle symbols, progression of DR was in the bars with arrow mark to the right, and the reduction in the stage was mentioned in the solid bars with arrow mark to the left. Number of patients per year with retained in the same stage was mentioned in the bottom as square box as shown in [Figure – 4]. Transition probability matrix was formed for changes between stages of DR. One year of TPM was 36 (81.8%) of 44 observations showed from stage-1 to stage-2, and 19 (21.3%) of 89 observations were showed the strength of relationship from stage-2 to stage-3 as shown in **[Table-2]**. Similarly, the probability of change from stage-2 to stage-3 was 0.40 and from stage-3 to stage-4 was 0.45. Again, the probability of change from stage-4 to the most severe stage-5 to stage-6 (PDR) was 0.70. Therefore, initially the chance of the increase in severity and similarly the chance of an increase at a more developed stage were very high. Moreover, the chance of moving from the other lower stages to higher was fairly high. After five years of TPM was observed that, the chance of moving from the other lower stages to the final stage was little bit increased. From this, it can be observed that with passage of time, the severity of DR increases. Nearly, 14 (17.7%) of 79 subjects with stage-3 or 4 DR changed into improved stage in between retina examinations.

## Discussion

Diabetic Retinopathy (DR) is one kind of the severe complication of DM. DR has been investigated by several researchers in developed and developing countries. In our present study, the mean duration of DM was fifteen years and above. Similar type of result was found by Klein et al. that nearly one third percentage of T2DM will get the development of DR over a period fifteen years of duration of DM. [24]

The duration of DM is significant with the development of macular edema also. This Edema progression in the retina causes vision loss in some of the DR. Due to clinically significant macular edema (CSME) occurs if there is thickening of center of the retina (macula) with more than five hundred µm or larger in size of the center of the retina. [25] In multiple linear regression analysis, age [34], $HbA_1C$, Duration of diabetics and other variables were found as statistically significant with DR. In many previous published articles, the similar type of results was found [26, 27, 30] and high level of $HbA_1C$ wasn't showed any statistically significant with retinopathy. [27] In another one study in Al-Naeem area of Kuwait by Al-Shammari et al has proved that the $HbA_1C$ level was a prominent risk factor for DR. [28] In this study, we have found LDL was significant with the development of DR. The same result was found in a study related to risk factors of retinopathy in T2DM patients in Pakistan by Hussain et al. [27] The duration of DM was a significant associated factor with DR was not significant has found in a study by Huseynova. [32]

**Table: 2 Distribution of one – year transition (Data) matrix among diabetic retinopathy patients after one year of progression**

| Severity Grade of Diabetic Retinopathy | No. of Observations | | | | | |
|---|---|---|---|---|---|---|
| | Severity Grade of Diabetic Retinopathy After One Year of Progression | | | | | |
| | 1 | 2 | 3 | 4 | 5 – 6 | Total |
| **1** | 8 | 36 | 0 | 0 | 0 | 44 |
| **2** | 19 | 22 | 38 | 10 | 0 | 89 |
| **3** | 3 | 10 | 16 | 20 | 2 | 51 |
| **4** | 0 | 4 | 6 | 5 | 13 | 28 |
| **5 – 6** | 0 | 0 | 0 | 0 | 38 | 38 |
| **Total** | 30 | 72 | 60 | 35 | 53 | 250 |

$\beta_0 = 148.840$, $X_1 = 1.035$, $X_3 = 1.387$, $X_4 = 13.631$, $X_5 = 0.787$, $X_7 = 1.750$, $X_8 = 33.831$, $X_9 = 1.027$. Substitute all values in equation (1), $Y = \beta_0 + \beta_1 X_1 + \beta_3 X_3 + \beta_4 X_4 + \beta_5 X_5 + \beta_7 X_7 + \beta_8 X_8 + \beta_9 X_9 = 528.5$ µm. Thus, the thickness of macular edema was 528.5 µm of a DR patient.

According to model – 2, totally 250 T2DM patients were included. In that, 125 (50%) patients were with DR and 125 (50%) patients without DR. 168 (67.2%) were male. The final binary logistic regression analysis, the following results have been obtained Hosmer-Lemeshow test for goodness of fit shows that the chi-square value was 8.43 with p-value > 0.05 wasn't significant, and this was proved that model was a good fit. Variables and their regression co-efficients and the level of significance were obtained by solving BLR Equation, $Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots \ldots \ldots + \beta_{11} X_{11} \ldots\ldots$ (1).

Example: Clinically significant variables of DM: $\beta_0 = 1.364$, $X_3 = 10.1$, $X_4 = 198$, $X_5 = 212$, $X_6 = 150$, $X_7 = 102$, $X_8 = 7$, $X_{11} = 1$. Then equation (1) was re-written as: $Y = \beta_0 + \beta_3 X_3 + \beta_4 X_4 + \beta_5 X_5 + \beta_6 X_6 + \beta_7 X_7 + \beta_8 X_8 + \beta_{11} X_{11}$; Substitute all the values, $Y = 1.364 + 0.175 + 1.246 + 0.102 + 0.240 + 0.200 + 0.018 + 0.041 = 3.386$ and odds ratio was P = 0.97. Finally concluded that, a DR patient having a chance to develop DR was 0.97.

According to model-3, data were obtained from DR patients in Aravind Eye Hospital. Among thirty DR patients, 22 (73.3%) were male. The average age participants 53.7 ± 6.7 years and average duration of DR was 7.42 ± 3.6 years. The estimator of coefficients of the cofactors were,

$$\hat{\beta}_1 = 0.1468;\ \hat{\beta}_2 = 0.1349;\ \hat{\beta}_3 = 0.0228$$

Solving the above equations, I have got the values $\alpha' = 0.033$ and $U = -1.783$; $\alpha' = (\alpha - 1)$ and $A = 1.033$

$$\hat{\alpha} = 1.033 \quad \text{and} \quad \hat{\beta} = 0.606$$

The chance of getting DR is very high for a DM person with covariate combination (1, 1, 1). The probability of developing DR is less probability with covariate (0, 0, 0) of a DM patient. Duration of DM of patient has to increases then progression of DR was also being increased by checking of stages of DR. Finally, I would find the probability of developing DR in the third, eighth, thirteen and Family history of DR was showed significant with the development of DR. Similar type of results was found a study related to DR in Northeastern Mexico by Cepeda-Nieto. [30] LDL was significant risk factor DR in our present study. Similar type of finding was found in a review article related on dyslipidemia and diabetic retinopathy by Chang. [31] A study by Ahmed et al. had revealed that hypertension was a significant risk factor of DR. [34] Similar result was found in our study. Triglycerides was significant in our present study. But in a study by Huseynova has showed there was no significant with DR. [32] The gender wasn't significant factor of DR. Similar type of result was revealed by Da Silva Correa et al. [33] HDL wasn't showed any statistically significant with DR. More similar type of result was found by Huseynova in the Baku City Hospital, Azerbaijan. [31]

Variables like $HbA_1C$, pre- and post-prandial blood sugar levels, systolic and diastolic blood pressure levels, duration of DM [34] and family history of incidence of DR have been found to play a significant ($p<0.05$) role in the probability of occurrence of DR. The propensity to the progression of DR is very less in southern region of India when compared with other regions. In this study, we found that the patient with diabetes normally twelve years and above those who are affected with DR. A similar type of result was found in a Saudi Arabian study by Ahmed et al. [34] that the duration of diabetes was found 13.4 years.

TPM [35] relating to transition of a person from one grade of severity of DR to the other grades after a period of one year. The probability of a patient from stage-1 to move to stage-2 was 0.82 which was very high. From this, we could understand, chance of severity of DR is very high at initial stage. But, in a study by Garg et al [36] has mentioned the probability in a DR patient moved from stage-1 to stage-2 was very less after one year.

## Conclusion

The present statistical models' studies were revealed that, the influencing factors for the development of DR from this one individual can identified their risk factors. The risk ratio has been computed which predict the chance of the development of DR of a T2DM patient. The number of years of DM is a prominent risk factor of the development of DR in a T2DM patient. The progression and transition of DR were increased by increasing by the duration of DM. A known diabetes patient can understand to know about their risk factors, what is their eye status and to know about DR stage in their both eyes, how to reduce their severity of stages of DR or to retain/protect in their same stage. So, the known diabetes patients with more duration of DM are directing to undergo regular checkups every six for their disease and severity of their eye with a trained ophthalmologist in a well-equipped eye hospital. Further studies have to be conducted related to these models with higher sample size in future.

**Authors' contributions:** **SV:** Conception and Study design; **SV:** Acquisition of Data, Data processing, Analysis and Interpretation of Data; **SV:** Drafting the article, revising it for intellectual content; Checked and approved of the final version of the manuscript.

**SV** – Senthilvel Vasudevan

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